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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 405/12, A61K 31/335, C07D 319/20 | A1

(11) International Publication Number: **WO 99/62902**

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/EP99/03648

(22) International Filing Date: 26 May 1999 (26.05.99)

(30) Priority Data:
9811879.7 3 June 1998 (03.06.98) GB

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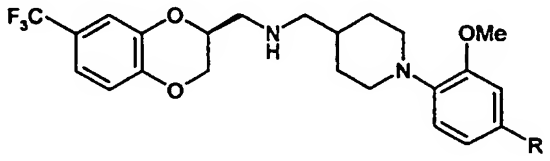
(81) Designated States: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HR, HU, ID, IL, IN, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: N–BENZODIOXANYLMETHYL–1–PIPERIDYL–METHYLAMINE COMPOUNDS HAVING AFFINITY FOR 5–HT RECEPTORS



(I)

(57) Abstract

Compounds of formula (I) including pharmaceutically acceptable salts thereof in which R represents H or F, their preparation and their use in the treatment of depression, anxiety, psychoses, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive–compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, migraine, non–insulin dependent diabetes melitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, drug–induced extrapyramidal symptoms or spasticity are described.

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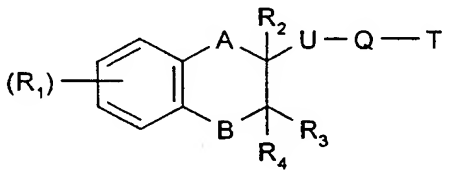
N-BENZODIOXANYLMETHYL-1-PIPERIDYL-METHYLAMINE COMPOUNDS HAVING AFFINITY FOR 5-HT RECEPTORS

The present invention relates to novel therapeutic agents which have affinity for 5-HT_{1A} and/or α_1 and/or D_2 receptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of central nervous system disorders, for example depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, migraine, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, drug-induced extrapyramidal symptoms and spasticity.

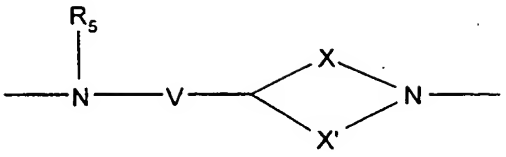
In WO93/17017 there are described [(benzodioxanyl, benzofuranyl and benzopyranyl)alkylamino]alkyl substituted 2-pyrimidinyl compounds which have vasoconstrictor activity. These compounds are claimed to be useful in treating conditions related to vasodilation.

In WO95/07274 compounds of formula I

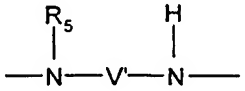


I

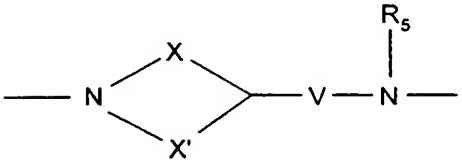
and pharmaceutically acceptable salts thereof in which A is methylene or -O-; B is methylene or -O-; and g is 0, 1, 2, 3 or 4; R_1 represents, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylthio, hydroxy, acyloxy, hydroxymethyl, cyano, alkanoyl, alkoxycarbonyl, optionally *N*-substituted carbamoyl, carbamoylmethyl, sulphamoyl or sulphamoylmethyl, an amino group optionally substituted by one or two alkyl groups, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring; R_2 is H, alkyl or alkoxy; R_3 and R_4, which are the same or different, are H, or alkyl; U is an alkylene chain optionally substituted by one or more alkyl; Q represents a divalent group of formula IIa, IIb or IIc



IIa



IIb

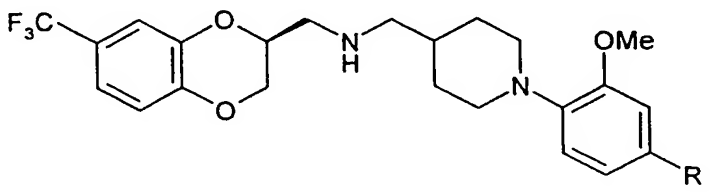


IIc

in which V is a bond or an alkylene chain optionally substituted by one or more alkyl; VN is an alkylene chain optionally substituted by one or more alkyl; X is a bond or an alkylene chain and X' is an alkylene chain, provided that the total number and carbon atoms in X and X' amounts to 3 or 4; R_5 is H, or alkyl; and T represents an optionally substituted aromatic group which optionally contains one or more N atoms, provided that T is not 2-pyrimidinyl when A is -O-; are disclosed as having utility in the treatment of central nervous system disorders, for example depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, and spasticity.

Surprisingly it has been found that certain compounds selected from the general disclosure of WO95/07274, but not specifically named or exemplified therein, exhibit increased activity and also increased selectivity compared to the compounds exemplified in WO95/07274.

The present invention provides compounds of formula I



I

including pharmaceutically acceptable salts thereof in which R represents H or F.

Specific compounds of the present invention are

(*S*)-(-)-1-[1-(4-fluoro-2-methoxyphenyl)piperid-4-yl]-*N*-(7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)methylamine
and
(*S*)-(-)-1-[1-(2-methoxyphenyl)piperid-4-yl]-*N*-(7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)methylamine

and pharmaceutically acceptable salts thereof.

The compounds of the present invention are advantageous over compounds known in the prior art because of their selectivity in receptor binding assays and their superior oral activity.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term active compound denotes a compound of formula I or a salt thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl- cellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the

compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof may be used to treat depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, migraine, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, drug-induced extrapyramidal symptoms and spasticity in human beings. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

The ability of compounds of formula I to interact with 5-hydroxytryptamine (5-HT) receptors has been demonstrated by the following test which determines the ability of the compounds to inhibit tritiated ligand binding to 5-HT receptors in vitro and in particular to 5-HT_{1A} receptors.

Hippocampal tissue from the brains of male Charles River CD rats weighing between 150-250 g were homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7) when measured at 25°C, 1:40 w/v) and centrifuged at 30,000 g at 4°C for 10 minutes. The pellet was rehomogenised in the same buffer, incubated at 37°C for 10 minutes and centrifuged at 30,000 g at 4°C for 10 minutes. The final pellet was resuspended in 50 mM Tris-HCl buffer (pH 7.7) containing 4 mM $CaCl_2$, 0.1% L-ascorbic acid and 10 μM pargyline hydrochloride (equivalent to 6.25 mg wet weight of tissue/ml) and used immediately in the binding assay. Aliquots (400 μl; equivalent to 2.5 mg wet weight of tissue/tube) of this suspension were added to tubes containing the ligand (50 μl; 2 nM) and distilled water (50 μl; total binding) or 5-HT (50 μl; 10 μM; non-specific binding) or test compound (50 μl; at a single concentration of 10^{-6} M or at 10 concentrations ranging from 10^{-11}-10^{-3} M). The ligand was [^{3}H]8-hydroxy-2-(dipropylamino)tetralin ([^{3}H]8-OH-DPAT) and the mixture was incubated at 25°C for 30 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting. The percentage displacement of specific binding of the tritiated ligand was calculated for the single concentration (10^{-6} M) of test compound. Displacement curves were then produced for those compounds which displaced ≥50% of specific binding of the tritiated ligand at 10^{-6} M using a range of concentrations of the compound. The concentration which gave 50% inhibition of specific binding (IC_{50}) was obtained from the curve. The inhibition coefficient Ki was then calculated using the formula

$$K_i = \frac{IC_{50}}{1+([ligand]/K_D)}$$

in which [ligand] is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The ability of compounds of formula I to interact with adrenoceptor binding sites has been demonstrated by the following test which determines the ability of the compounds to inhibit tritiated ligand binding to adrenoceptors in vitro and in particular α_1-adrenoceptors.

Whole cortical tissue from the brains of male Charles River CD rats weighing between 150-250 g were homogenised in ice-cold 50 mM Tris-HCl, pH 7.6 (at 25°C; 1:40 w/v) and centrifuged at 1000 g at 4°C for 10 minutes. The supernatant was centrifuged at 30,000 g at 4°C for 10 minutes. The pellet was rehomogenised in 50 mM Tris-HCl, pH 7.6 (1:40 w/v) and centrifuged at 30,000 g at 4°C for 10 minutes. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.6 (equivalent to 12.5 mg wet weight of tissue/ml) and used immediately in the binding assay. Aliquots (400 µl; equivalent to 5 mg wet weight of tissue/tube) of this suspension were added to tubes containing the ligand (50 µl; 0.1 nM) and distilled water (50 µl; total binding) or phentolamine (50 µl; 5 µM; non-specific binding) or test compound (50 µl; at a single concentration of 10^{-6}M or at 10 concentrations ranging from 10^{-11} - 10^{-3}M). The ligand was [7-methoxy-^{3}H]prazosin and the mixture was incubated at 30°C for 30 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting. The percentage displacement of specific binding of the tritiated ligand was calculated for the single concentration (10^{-6} M) of test compound. Displacement curves were then produced for those compounds which displaced ≥50% of specific binding of the tritiated ligand at 10^{-6} M using a range of concentrations of the compound. The concentration which gave 50% inhibition of specific binding (IC_{50}) was obtained from the curve. The inhibition coefficient Ki was then calculated using the formula

$$K_i = \frac{IC_{50}}{1+([ligand]/K_D)}$$

in which [ligand] is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The ability of compounds of formula I to interact with dopamine receptors has been demonstrated by the following test which determines the ability of the compounds to inhibit tritiated ligand binding to dopamine receptors in vitro and in particular to the D_2 dopamine receptors.

Striatal tissue from the brains of male Charles River CD rats weighing between 140-250 g were homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7 when measured at 25°C) and centrifuged at 40,000 g for 10 minutes. The pellet was resuspended in Tris salts buffer (50 mM Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$ with the addition of 6 mM ascorbic acid; pH 7.7 when measured at 25°C), and again centrifuged at 40,000 g for 10 minutes. The final pellet was stored at -80°C. Before each test the pellet was resuspended in Tris salts buffer (equivalent to 2 mg wet weight of tissue/ml). Aliquots (720 µl; equivalent to 1.44 mg wet weight of tissue/tube) of this suspension were then added to tubes containing the ligand (40 µl; 1 nM) and Tris salts buffer (40 µl; total binding) or spiroperidol (40 µl; 10 nM; non-specific binding) or test compound (40 µl; at a single concentration of 10^{-6}M or at 6 concentrations ranging from 10^{-11}-10^{-4}M). The ligand was tritiated (*S*)-sulpiride and the mixture was incubated at 4°C for 40 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out in to vials, scintillation fluid added and were left for about 20 hours before being counted by scintillation spectrophotometry. The percentage displacement of specific binding of the tritiated ligand was calculated for the single concentration (10^{-6} M) of test compound. Displacement curves were then produced over a range of concentrations for those compounds which displaced ≥50% of specific binding of the tritiated ligand at 10^{-6}M. The concentration which gave a 50%

inhibition of specific binding (IC_{50}) was obtained from the curve. The inhibition coefficient Ki was then calculated using the formula

$$K_i = \frac{IC_{50}}{1+([ligand]/K_D)}$$

in which [ligand] is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The K_i values obtained in the above tests for 5-HT_{1A}, α_1 and D_2 binding for each of the final products of Examples 1, 2, and Comparative ExampleA are given in Table I below. It is clear from these data that compounds of the present invention have significantly less affinity for the α_1 adrenoceptor than compounds previously described. This is important as it is known in the art that α_1 receptor antagonism mediates serious side-effects such as hypotension, sedation and sexual dysfunction. Thus, compounds which interact preferentially with D_2 and 5-HT_{1A} receptors whilst having less interaction with α_1 receptors are advantaged.

TABLE 1

Example Number	Ki (nM) value for		
	5-HT_{1A}	D_2	α_1
1	23	65	183
2	31	54	404
A	22	44	53

Antagonism of Apomorphine-Induced Climbing in Mice

Groups of 10 male mice weighing 18-35 g (max. range 10 g) were treated with test compound or control vehicle by po administration. 30 minutes later, mice were injected subcutaneously with apomorphine (0.88 mg/kg). Immediately after the apomorphine injection the mice were placed in the test cages and the climbing

behaviour of each mouse was assessed at 10 and 20 minutes on a simple 0-2 ranking scale.

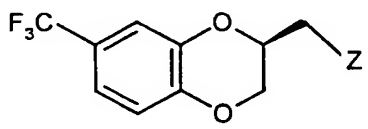
The ED_{50} values (dose causing 50% of the control score) for the test compounds and 95% confidence limits were calculated. ED_{50} values are calculated as free base equivalents and are given in Table 2 alongside Comparative Example A. The compounds of the present invention are more potent orally than compounds previously described. More potent compounds are advantaged as they are less likely to induce systemic toxicological effects on organs which are not the therapeutic target.

TABLE 2

Example	ED_{50} (mg/kg)
1	1
2	1.8
A	5

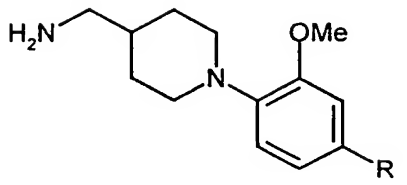
Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention. The processes are preferably carried out at atmospheric pressure, at a temperature in the range 0-200°C, preferably in the range 20-150°C. The substituents are as defined for formula I above unless otherwise stated.

Compounds of formula I may be prepared by reacting a compound of formula II



II

in which Z is a leaving group, for example toluene-4-sulphonyloxy, with a compound of formula III



III

in which R is as previously defined, optionally in the presence of a suitable solvent or mixture of solvents, for example a hydrocarbon, eg toluene, or a polar solvent, eg dimethylformamide, or mixtures thereof, optionally in the presence of a base, for example potassium carbonate at a temperature in the range of 0 – 250°C.

The invention is illustrated by the following Examples which are given by way of example only. The final product of each of these Examples was characterised by one or more of the following procedures: gas-liquid chromatography; high performance liquid chromatography; elemental analysis, nuclear magnetic resonance spectroscopy and infrared spectroscopy.

Example 1

Part A

a) A solution of 5-fluoro-2-nitrophenol (25.0 g) in dry dimethylformamide (100 ml) was added dropwise with stirring over 1 hour to a suspension of sodium hydride (7.0 g of a 60% dispersion in mineral oil) in dry dimethylformamide (250 ml) under nitrogen. The mixture was stirred for 1 hour and then iodomethane (10.0 ml) was added dropwise to the mixture. The mixture was then stirred and heated on a steam bath for 3.5 hours. Further iodomethane (2.5 ml) was added and the mixture was stirred at 95-100°C for 1 hour and then allowed to cool overnight. Concentrated aqueous ammonia solution (15.0 ml; S.G. 0.880) was added dropwise and the mixture was stirred for 15 minutes. The mixture was poured into water (1.5 l) basified with aqueous sodium hydroxide solution (5M) and extracted with dichloromethane (4 x 400 ml). The combined organic extracts were washed with water, brine, dried, filtered and evaporated to give a liquid which was dissolved in ether (500 ml), washed with water, brine, dried, filtered and evaporated to give an oil which was again dissolved in ether and the previous washing and drying process repeated to give an oil which was triturated with petroleum ether, b.p. 60-80°C, and allowed to

stand overnight. The solid produced was collected by filtration and dried in vacuum to give 4-fluoro-2-methoxynitrobenzene. The structure was confirmed by ^{1}H nmr.

b) A solution of 4-fluoro-2-methoxynitrobenzene (23.7 g) in industrial methylated spirits (400 ml) was hydrogenated at ambient temperature using 10% palladium on charcoal as the catalyst. After the theoretical uptake of hydrogen, the mixture was filtered to remove the catalyst and the filtrate was evaporated to give 4-fluoro-2-methoxyaniline as an oil.

c) A mixture of 4-fluoro-2-methoxyaniline (5.7 g) and 4-carbamoyl-1-(2,4-dinitrophenyl)pyridinium chloride (22.4 g, prepared as described in WO95/07274) and methanol (350 ml) was stirred and boiled under reflux for 2 hours. The mixture was cooled in an ice-water bath and filtered. The filtrate was evaporated under reduced pressure to give a solid which was triturated with boiling acetone (900 ml). The mixture was allowed to cool and the product collected by filtration and washed with acetone to give 4-carbamoyl-1-(4-fluoro-2-methoxyphenyl)pyridinium chloride.

d) The product from c) (13.2 g), ammonium formate (26.6 g) and 10% palladium on charcoal (6.6 g) were stirred under nitrogen whilst industrial methylated spirits (250 ml) was added. The mixture was stirred vigorously and boiled under reflux under nitrogen for 3.5 hours with sublimed ammonium formate being washed back into the reaction vessel with water. The mixture was allowed to cool then filtered through a filtration aid which was washed with industrial methylated spirits, ethyl acetate and water. The filtrate was evaporated under reduced pressure and the residue was partitioned between water (1 l) and ethyl acetate (500 ml). The mixture was made strongly alkaline with 5M sodium hydroxide solution. The aqueous layer was separated and extracted with ethyl acetate (3 x 500 ml). The combined ethyl acetate extracts were dried, filtered and evaporated to give 1-(4-fluoro-2-methoxyphenyl)piperidine-4-carboxamide.

e) The product from d) (10.4 g) was suspended in tetrahydrofuran (300 ml) and added in portions with stirring to a suspension of lithium aluminium hydride (3.4 g) in tetrahydrofuran (100 ml) under nitrogen in an ice-water bath. The mixture was stirred in an ice-water bath for 1.5 hours then stirred at ambient temperature for 19 hour.

Water (20 ml) was added cautiously to the reaction mixture followed by 5M sodium hydroxide solution (20 ml) and water (40 ml). The mixture was stirred for 1 hour then filtered through a filtration aid, washing the aid with ether (700 ml). The filtrate was separated and the organic phase was dried, filtered and evaporated to give a gum which was triturated with dichloromethane (100 ml) and filtered to remove some solid. The filtrate was evaporated to give an oil which was purified by flash column chromatography on silica using methanol followed by methanol/triethylamine (10:1) as the mobile phase. Appropriate fractions were collected, combined and evaporated to give 1-(4-fluoro-2-methoxyphenyl)piperidine-4-methylamine.

Part B

a) Hexamethylenetetramine (47.5 g) was added portionwise to a stirred solution of 4-trifluoromethylphenol (50 g) in trifluoroacetic acid (680 ml) and the mixture was heated at reflux temperature for 24 hours. After cooling, water (355 ml) was added followed by aqueous sulphuric acid (50% v/v, 190 ml) and the reaction was stirred at ambient temperature for 4 hours. The acidic aqueous phase was extracted with diethyl ether (3 x 500 ml). The combined organic extracts were washed with hydrochloric acid (5M, 3 x 500 ml) then water (500 ml) and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica eluting with a 4:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate. The appropriate fractions were combined and the solvent removed under reduced pressure to give 5-trifluoromethyl-2-hydroxybenzaldehyde (25 g) as a light pink solid.

b) A mixture of (*R*)-glycidyl 4-toluenesulphonate (24 g), 5-trifluoromethyl-2-hydroxybenzaldehyde (20 g) and potassium carbonate (16 g) in dimethylformamide (550 ml) was stirred and heated at 60°C for 72 hours. After cooling, brine (1.5 l) was added and the resultant mixture extracted with ether (4 x 500 ml). The combined ether extracts were washed with brine (2 x 500 ml), then water (500 ml) and dried over magnesium sulphate. The residue was purified by flash column chromatography on silica eluting with a 3:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate to give (*R*)-5-trifluoromethyl-2-(2,3-epoxypropoxy)benzaldehyde (18.7 g) as a yellow oil.

c) A mixture of the product from the previous reaction (18.7 g) and 3-chloroperoxybenzoic acid (57-86%, 48.7 g) in dichloromethane (1 l) was heated under reflux for 24 hours then allowed to cool to ambient temperature. The mixture was washed with saturated aqueous sodium bicarbonate (3 x 700 ml), water (2 x 700 ml) and brine (700 ml), then dried over magnesium sulphate. The solvent was evaporated to give crude (*R*)-5-trifluoromethyl-2-(2,3-epoxypropoxy)phenyl formate (16.7 g).

d) A mixture of the product from the previous reaction (16.7 g), tetrahydrofuran (220 ml) and a saturated aqueous potassium carbonate solution (175 ml) was stirred vigorously at ambient temperature for 24 hours. Water (500 ml) was added and the organic phase was removed. The aqueous phase was extracted with ethyl acetate (3 x 300 ml) and the combined organic extracts were dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica eluting with a 4:1 grading to 1:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate. Appropriate fractions were combined and the solvent was removed under reduced pressure to give (*S*)-7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (12 g) as a yellow oil.

e) A solution of 4-toluenesulphonyl chloride (9.6 g) in dichloromethane (60 ml) was added dropwise to a solution the product from the previous reaction (10.7 g) and 4-dimethylaminopyridine (6.7 g) in dichloromethane (90 ml) between 0-5°C. The mixture was stirred at ambient temperature for 4 hours then allowed to stand for 18 hours. The solution was washed with dilute hydrochloric acid (5M, 2 x 300 ml) dried over magnesium sulphate and the solvent was removed under reduced pressure to afford (*R*)-7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl 4-toluene-sulphonate (15.5 g) as a white solid.

Part C

The 4-toluenesulphonate from Part B (e) (4.3 g), the methylamine from Part A (e) (2.4 g), potassium carbonate (2.4 g), toluene (80 ml) and dimethylformamide (30 ml) were stirred and boiled under reflux for 24 hours. The mixture was allowed to

cool, poured into water (1.5 l) and then extracted into ethyl acetate (3 x 350 ml). The combined organic extracts were extracted with 5M hydrochloric acid (3 x 250 ml). The combined acidic extracts were basified with 5M sodium hydroxide solution and extracted with ethyl acetate (3 x 250 ml) and these organic extracts were dried, filtered and evaporated to give an oil. This oil was dissolved in ether (100 ml) and dried over potassium carbonate. The mixture was filtered and evaporated to give an oil which was purified by flash column chromatography on silica using ethyl acetate/ petroleum ether, b.p. 60-80°C (9:1) as the mobile phase. Appropriate fractions were collected, combined, and evaporated to give an orange oil which was dissolved in ether (100 ml) and hydrogen chloride gas was bubbled through the solution for 15 minutes. A precipitate which formed was collected by filtration and dried under vacuum at 80°C for 23 hours to give (*S*)-(-)-1-[1-(4-fluoro-2-methoxyphenyl)piperid-4-yl]-*N*-(7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)methylamine dihydrochloride, m.p. 230-231°C.

Example 2

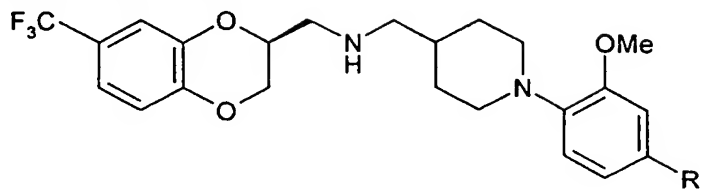
A mixture of 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (3.3 g, prepared as described in WO95/07274), (*R*)-7-trifluoromethyl-1,4-benzodioxan-2-ylmethyl 4-toluene sulphonate (3.0 g), potassium carbonate (2.5 g), toluene (22 ml) and dimethylformamide (10 ml) was boiled under reflux for 18 hours with stirring. The mixture was cooled, poured into water (100 ml) and extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (2 x 200 ml) and the acidic extracts were basified with concentrated sodium hydroxide solution and then extracted with ethyl acetate (200 ml). These organic extracts were dried, filtered and evaporated to give an oil which was purified by flash column chromatography on silica using ethyl acetate/methanol (95:5) as the mobile phase to give an oil which was treated with hydrogen chloride gas as described in Example 1 to give (*S*)-(-)-1-[1-(2-methoxyphenyl)piperid-4-yl]-*N*-(7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)methylamine dihydrochloride, m.p. 243-245°C with decomposition.

Comparative Example A

(S)-(-)-*N*-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-(1-(2-methoxyphenyl)piperid-4-yl)methylamine (also known as (S)-(-)-*N*-(7-chloro-2,3-dihydro-1,4-benzodioxin-2-methyl)-1-(1-(2-methoxyphenyl)piperid-4-yl)methylamine) was prepared as described in WO 95/07274.

Claims

1. Compounds of formula I



I

including pharmaceutically acceptable salts thereof in which R represents H or F.

2. A compound according to claim 1 which is (*S*)-(-)-1-[1-(4-fluoro-2-methoxyphenyl)piperid-4-yl]-*N*-(7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-methylamine and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 which is (*S*)-(-)-1-[1-(2-methoxyphenyl)-piperid4yl]-*N*-(7-trifluoromethyl-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)methylamine and pharmaceutically acceptable salts thereof.

4. Pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1-3, together with a pharmaceutically acceptable diluent or carrier.

5. A method of treating depression, anxiety, psychoses, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, migraine, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, drug-induced extrapyramidal symptoms or spasticity which comprises the administration of a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1-3 to a patient in need thereof.

6. A method as claimed in claim 5 for treating schizophrenia.

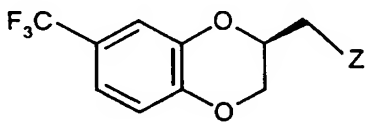
7. A method as claimed in claim 5 for treating anxiety.

8. A compound of formula I as claimed in any one of claims 1-3 for use as a medicament.

9. A compound of formula I as claimed in any one of claims 1-3 for use as a medicament for treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, migraine, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, drug-induced extrapyramidal symptoms or spasticity.

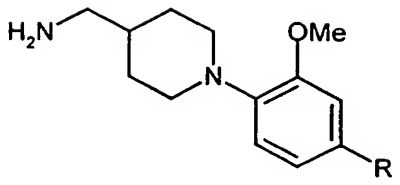
10. The use of a compound of formula I as claimed in any one of claims 1-3 in the manufacture of a medicament for treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, migraine, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, drug-induced extrapyramidal symptoms or spasticity.

11. A process for preparing compounds of formula I according to claim 1 comprising reacting a compound of formula II



II

in which Z is a leaving group with a compound of formula III



III

in which R is as previously defined, optionally in the presence of a suitable solvent or mixture of solvents, optionally in the presence of a base, at a temperature in the range of 0 –250°C.

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/03648

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D405/12 A61K31/335 C07D319/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical. search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 1999	30/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Engl, B

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/03648

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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